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Nature's Nurturers: Unveiling the Healing Power of Medicinal Mushrooms in Accelerating Wound Recovery

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ABSTRACT

Medicinal mushrooms have been used in traditional medicine for a long time due to their various health benefits, particularly in wound healing. This article delves into their capabilities in healing wounds, with a specific focus on important bioactive components like chitin and chitosan, polysaccharides, and the transition from ethnobiology to ethnopharmacology. Recent progress in comprehending the wound-healing properties of medicinal mushrooms emphasizes the significance of chitin and chitosan, which are abundant in the cell walls of fungi. These compounds possess antimicrobial, anti-inflammatory, and immunomodulatory effects, which aid in wound closure, reducing infection rates, and promoting tissue regeneration. The combination of these bioactive molecules with other substances found in mushrooms presents promising opportunities for future wound-healing therapies. The integration of traditional knowledge and scientific research highlights the potential of medicinal mushrooms in the development of innovative and effective treatments for wound healing. Ongoing investigation into the mechanisms and applications of these bioactive compounds holds great promise for advancing wound care.

Keywords: Mushroom, chitin and chitosan, polysaccharides, ethnobiology, ethnopharmacology, and wound healing

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INTRODUCTION

Mushrooms, categorized as macrofungi, encompass a vast array of species, primarily consisting of basidiomycetes and some ascomycetes [1-3]. The number of mushroom species on Earth is astonishing, estimated to be 140,000 [4], with approximately 22,000 of them identified so far [2]. Throughout history, mushrooms have held great significance in various cultures worldwide, being highly esteemed for their nutritional and medicinal properties. Their extensive use is particularly notable in Asian, Northern, and Central American countries, where they have been integrated into traditional practices for centuries [5]. These filamentous fungi, known for their unique fruiting bodies, offer numerous pharmacological benefits for human health. Apart from being delicious culinary ingredients, mushrooms have long been recognized for their medicinal properties. The diverse range of pharmacological aspects found in mushrooms has made them an asset in promoting human well-being. Presently, mushrooms are extensively cultivated globally, contributing not only to gastronomic delights but also serving as an essential component of the human diet. Their historical legacy is deeply ingrained in their dual roles as both nourishment and medicine [6,7,8].

Mushrooms offer numerous benefits as a source of functional foods and natural molecules. They can be cultivated in both the fruiting body and mycelium forms, and produce bioactive components quickly, with the potential for optimization through manipulation. From a nutritional standpoint, mushrooms are high in protein and low in fat and contain significant amounts of vitamins B, C, D, and K, minerals like potassium and phosphorus, and trace elements such as selenium. They also provide dietary fibers and functional components like chitin and beta-glucans [9,5,10].

For centuries, civilizations such as Ancient China, Eastern Europe, Mesoamerica, and Africa have recognized the medicinal properties of mushrooms and utilized them for the benefit of humans. These mushrooms have been found to possess various therapeutic effects, including antitumor, antibacterial, and antiviral properties, thanks to their bioactive compounds [11,12].

In the field of modern biomedical sciences, there is a growing interest in discovering new and effective compounds that can enhance wound healing. Researchers are increasingly focusing on phyto medicine, which harnesses the natural healing pathways of plants to treat wounds. Surprisingly, over 70% of pharmaceutical products for wound healing are derived from plants, while only 20% rely on mineral compounds [12,13].

Given the wide range of vital therapeutic properties exhibited by higher fungi, more attention has been drawn to mushrooms. However, the complete understanding of mushrooms' ability to heal wounds is still lacking. Therefore, it is crucial to study the effects of mushrooms on wound healing. The outcomes of such studies are heavily influenced by factors such as the type and strain of the fungus, the composition of the culture medium used for cultivation, the specific part of the fungus utilized (spores, mycelia, fruit bodies), and the methods employed to extract its active ingredients (including the medium used for suspension and the extractant) [11-13]. The wound healing capabilities of mushrooms involve various mechanisms, including the stimulation of immune epithelial cells, as well as the release of cytokines and growth factors [14,15]. Hence, considering the aforementioned factors, this present analysis aims to provide substantial insights into the nutritional worth and makeup of mushrooms, along with their ethnobiology and ethnopharmacology, and their potential in the healing of wounds.

Medicinal Potentials Hidden in Mushrooms

Figure 1: Different Varieties of Mushrooms and Their Health Benefits.

Mushrooms are rich in a wide range of nutritional and medicinal bio-components, making them valuable for improving public health globally. They are packed with various bioactive substances that have beneficial effects such as reducing tumor growth, lowering cholesterol levels, boosting the immune system, fighting against oxidative stress, preventing microbial infections, and reducing inflammation. These compounds include polysaccharides, complex molecules like polysaccharide-proteins and polysaccharide-peptides, ribonucleases, proteases, and lectins.

Several secondary metabolites of low molecular weight, including lactones, terpenoids, alkaloids, and antibiotics with different chemical groups, as well as metal-chelating agents, are among the other compounds of therapeutic importance [45] Extracted from the crude extracts of mycelia and fruiting body of medicinal mushrooms, compounds such as α–β-unsaturated polysaccharides, glycoproteins, peptides, phenolic derivatives, hydrolytic, lipids, and oxidative enzymes have demonstrated healing properties. These mushrooms, known as 'mushroom nutraceuticals', are often consumed in the form of capsules or tablets as nutritional supplements, which are derived from their extract or dried biomass of mycelium. Regular intake of such nutraceuticals prepared from mushrooms has been observed to enhance the immune response of the body and improve disease conditions [46].

Chaga Mushroom

Often hailed as the "monarch" of medicinal fungi, Chaga (derived from the Russian tschaga) is a rare fungus that thrives in the frigid climates of North America, northern Europe, and Russia. Despite its unconventional appearance a misshapen, jet-black parasitic mass clinging to the bark of hardwood trees chaga possesses remarkable healing potential beneath its charred exterior [16]. Chaga mushrooms boast a wealth of antioxidants and anti-inflammatory compounds, such as betulinic acid and ergosterol, which contribute to the reduction of inflammation. Numerous studies conducted on mice have demonstrated the anti-inflammatory effects of Chaga extract, revealing its ability to inhibit the production of pro-inflammatory cytokines.

Cytokines, being small protein-based signaling molecules, serve as a means of cellular communication. It is important to note that not all cytokines are detrimental. Research indicates that chaga exhibits formidable anti-cancer properties, capable of suppressing the growth of malignant cells. Furthermore, its antibacterial and antiviral attributes make it a potent supporter of the immune system, aiding in the defense against harmful pathogens without any toxic side effects [17,18].

Cordyceps

Cordyceps, a parasitic fungus that thrives on the larvae of the Himalayan bat moth, is a rare and valuable resource highly sought after in both traditional medicine and the global market. Renowned for its aphrodisiac properties, it has earned the moniker "Himalayan Viagra." Additionally, it is believed to possess anti-inflammatory, antioxidant, and immune-boosting effects. In the realm of traditional medicine, yarsagumba has been utilized to address a wide array of ailments, including respiratory disorders, kidney problems, and fatigue. Moreover, it is thought to possess wound-healing properties, with certain studies indicating its potential to expedite the healing process and alleviate inflammation. One possible mechanism through which yarsagumba promotes wound healing is by stimulating collagen production, a vital protein for new tissue formation. Furthermore, it may enhance blood circulation to the affected area, thereby accelerating the delivery of nutrients and oxygen to the site of the wound [18].

Red Reishi

Red Reishi, scientifically known as Ganoderma lucidum, is a mushroom variety deeply rooted in traditional Chinese medicine for countless years. Its extensive usage is attributed to its numerous health advantages, particularly in wound healing. A study featured in the Journal of Ethnopharmacology highlights the remarkable wound-healing capabilities of Red Reishi. This mushroom is renowned for its anti-inflammatory and antioxidant properties, which effectively alleviate inflammation and facilitate the healing process. Additionally, it is believed to enhance the immune system, enabling it to combat infections and expedite the recovery process [19,20].

Previous research has indicated that G. lucidum could regulate the microbiota in the gut, suggesting the potential to regulate microbiota in other organisms [21]. A growing body of literature has shown a connection between immunoregulation, inflammation, and organismic microbiota [22, 23]. The skin is home to a variety of microorganisms, including bacteria, fungi, viruses, mites, and the skin microbial community has the potential to impact the immune function of the skin [24]. Additionally, the skin microbiota may influence wound healing through pattern-recognition receptors (PRRs) [25]. Toll-like receptor 4 (TLR4), which is one of the PRRs, plays a crucial role in the innate immune system [26]. Understanding the role of TLR4 in the relationship between skin microbiota and skin wound healing is of great importance, although limited research has been conducted in this area [27]. This study aimed to uncover the underlying mechanism of Constituents in promoting wound healing.

Shiitake

For centuries, traditional medicine has recognized the healing properties of shiitake mushrooms. These mushrooms contain various bioactive compounds that possess anti-inflammatory, antioxidant, and antimicrobial properties. A recent study conducted on rats with oral ulceration discovered that the administration of LEP (polysaccharides extracted from shiitake) had a significant impact. It notably increased the activity of antioxidant enzymes in the bloodstream, while simultaneously reducing levels of interleukin–2 (IL–2) and tumor necrosis factor alpha (TNF–a) in both the bloodstream and mucosal tissues. These findings suggest that shiitake mushrooms may have a beneficial role in wound healing [28,29].

Oyster mushrooms

Oyster mushrooms, a variety of edible fungi, have been utilized across various cultures for centuries. They possess remarkable nutritional value and offer a multitude of health advantages, including the enhancement of skin health. Oyster mushrooms are rich in essential vitamins and minerals such as zinc, iron, selenium, potassium, and vitamin B12, all of which contribute to the proper functioning of the skin. Moreover, these mushrooms possess anti-inflammatory properties that can assist in the healing of wounds when applied topically. They contain beta-glucans, which are polysaccharides that aid in maintaining optimal collagen levels for healthy skin. Additionally, oyster mushrooms are believed to possess antiviral, immunomodulating, antioxidant, anti-hypercholesterolemia, and anti-diabetic properties [30,31].

Turkey tail (Trametes versicolor or Coriolus versicolor)

Turkey tail, also known as tunzhi in China or Coriolus versicolor, has long been revered as a medicinal herb in Asian regions, particularly in China. It is rich in antioxidants and other compounds that promote good health. Studies have shown that turkey tail extract can boost the immune system, aiding in the healing of wounds. The presence of polysaccharopeptides and beta-glucans in the extract enhances immune system function. Additionally, the antioxidants in turkey tail extract counteract harmful free radicals, reducing oxidative stress. Moreover, turkey tail extract promotes collagen synthesis, which facilitates the production of new connective tissue and speeds up wound closure.

By stimulating collagen production and strengthening the wound bed, turkey tail extract helps minimize scarring and improves healing outcomes. This, in turn, reduces the risk of complications. Cellular regeneration plays a crucial role in wound healing, as new cells are needed to replace damaged or dead cells. Turkey tail extract contains bioactive compounds that can stimulate the growth and movement of various cell types involved in wound healing, such as fibroblasts and keratinocytes.

Furthermore, turkey tail extract has been found to enhance the formation of granulation tissue, an essential step in wound healing. Granulation tissue acts as a framework for new blood vessels and aids in the formation of new skin [32,33,34].

Enokitake (Flammulina Velutipes)

Enokitake mushrooms, also known as Flammulina velutipes, are a popular and globally cultivated species of mushrooms. They have a long history in traditional medicine and are valued for their potential health benefits. One of the key components of enokitake mushrooms is their polysaccharide content, which has been found to enhance the immune system and protect against infections and diseases. These mushrooms also possess antioxidant properties, which can reduce the risk of chronic diseases caused by free radicals. Additionally, enokitake mushrooms have been associated with promoting cardiovascular health by regulating cholesterol levels and blood pressure. They can also protect the liver and support its function. Lastly, enokitake mushrooms help maintain a balanced inflammatory response in the body, which is important for overall health [35-42].

Yellow Morel (Morchella Esculenta)

Yellow Morels, scientifically identified as Morchella esculenta, are a type of medicinal mushroom deeply rooted in traditional medicine practices spanning centuries. Their medicinal properties are often attributed to the rich content of active polysaccharides. Extracts obtained from these mushrooms encompass a polysaccharide-protein complex that holds promise for a wide array of therapeutic applications, contributing to overall human health. The presence of polysaccharides and phenolic compounds in Yellow Morels imparts antioxidant and anti-cancer properties [43].

A comprehensive review article featured in Current Research in Environmental & Applied Mycology underscores the historical utilization of Yellow Morels by local communities. These communities employ the mushroom's fruiting bodies to address a range of health concerns, including stomach pain, pneumonia, respiratory issues, and wound healing. While existing research points to the potential wound-healing activity of Yellow Morels, further investigation is imperative to isolate and identify additional bioactive compounds responsible for these therapeutic effects [44].

Mycology Unveiled: Mushrooms' Ethnobio to Ethnopharmacology

Mushrooms consist of a fruiting body comprising a cap (pileus), gills (lamellae), stalk (stipe), and mycelium, which absorbs nutrients [45]. Historically, mushrooms were categorized as part of the plant kingdom, but current taxonomy recognizes fungi as a distinct group under the Mycota kingdom, primarily due to the presence of chitin in their cell walls. While wild mushrooms are seasonal and harvested for use, they can also be cultivated through spore culture in figure (2).

Mushrooms possess a mysterious composition, with umami-flavored, medicinal, hallucinogenic/psychoactive, and poisonous compounds. Moreover, certain fungal species can also store heavy metals in their fruit bodies. Currently, the most popular mushrooms known for their significant health benefits are Chaga (Inonotus obliquus), Cordyceps (Cordyceps sinensis), Lion's Mane (Hericium erinaceus), Reishi (Ganoderma lucidum), Shiitake (L. edodes), and Turkey Tail (Trametes versicolor).

Mushrooms serve as a rich source of immunomodulating biomolecules, with proven clinical benefits in treating cancer, infectious diseases, and immunological disorders [46,47]. These fungi contain immunostimulant compounds like b-glucans, polyinosinic: polycytidylic acid, and lip polysaccharide, which enhance immune system function. Additionally, mushrooms' folate content contributes significantly to DNA synthesis and repair [48]. Currently, more than 270 fungal species are recognized for their diverse biological activities, including adaptogenic, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, and hypocholesterolemic properties. With the increasing cultivation of mushrooms for food, they are increasingly utilized as dietary supplements to combat various diseases and associated health issues [49]. Furthermore, studies have indicated that mushrooms possess various beneficial properties such as anti-atherogenic, hepatoprotective, antinociceptive, anti-inflammatory, antidiabetic, and antioxidant effects [50,51,52]. Over the past few decades, extensive scientific research has been conducted in Japan, China, Korea, and more recently in the United States, highlighting the potential of mushrooms in the prevention and treatment of chronic diseases including cancer, hypertension, and heart disease [53,54,55]. In certain Asian countries, mushroom extracts are even consumed as adjuvant care in cancer treatment, alongside other therapies [56].

Internationally, several organizations have given their approval for the consumption of different mushroom species in the form of dietary supplements. These organizations include the European Novel Food Regulations, Complementary Medicine in the UK, National Health Service, German Federal Health Agency, Japan Foods for Specific Health Use (FOSHU), which is the largest in the world, and various organizations in the USA such as the Federal Food Drug and Cosmetic Act, Dietary Supplement Health and Education Act (DSHEA), National Institute of Health (NIH), and American Herbal Products Association (AHPA) [57]. Numerous studies have been conducted by specialized centers to explore the potential benefits of these mushrooms in the treatment of various cancers, acquired immunodeficiency syndrome (AIDS), and other illnesses related to an imbalanced immune system. Additionally, research on certain mushroom species has demonstrated their ability to support the body in the synthesis of interferon [58].

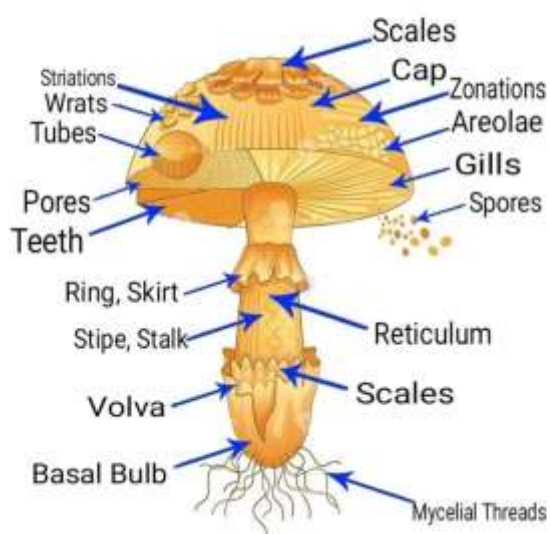

Figure 2: Mushroom Anatomy: Nature's Intricate Design [138]

Chemical Compounds: The Healing Power of Mushroom Menders.

Mushrooms not only provide a delectable flavor to dishes, but they also contain a wealth of bioactive compounds that improve nutritional value and provide medicinal advantages. Some of these compounds play a key role in promoting the healing of wounds:

Polysaccharides:

Glycosaminoglycan (GAG) or mucopolysaccharides play significant roles in various cellular processes such as cell signaling, development, angiogenesis, anticoagulation, and acting as co-receptors for growth factors. These molecules are crucial in regulating all phases of wound healing, including both acute and severe wounds. GAG is a complex structure consisting of carbohydrate molecules that interact with multiple proteins involved in physiological and pathological processes [59, 60]. With a molecular weight ranging from 10 to 100 kDa, GAG is a linear polysaccharide with a negative charge. This electrostatic property is beneficial in controlling excessive protease production by forming ion pairs with cationic neutrophils and interfering with the activity of these cationic proteins through charge interactions [61]. By reducing excessive neutrophil recruitment and protease production, the wound can efficiently transition from the inflammatory stage to the subsequent healing stage, particularly in cases of severe wound injuries.

Terpenoids:

Terpenoids, naturally occurring hydrocarbons produced by a wide range of plants and animals, have a significant impact on wound healing. Let's explore their importance in more detail:

Anti-Inflammatory Properties:

Terpenoids possess anti-inflammatory effects, which can be highly beneficial during the healing process of wounds. By reducing inflammation, they create an optimal environment for tissue repair and regeneration [62].

Antimicrobial and Antifungal Effects:

Certain terpenoids exhibit antimicrobial and antifungal properties. These properties help prevent infections at the site of the wound, thereby promoting faster healing [63].

Skin Permeation Enhancement:

Terpenoids are utilized as skin permeation enhancers. They facilitate the absorption of therapeutic agents through the skin, which can be advantageous for wound healing treatments [64].

Stimulation of Repair Agents:

Terpenoids can activate and attract various cells involved in wound healing. For example:

- Platelets: Packed with growth factors, platelets attract neutrophils, macrophages, endothelial cells, and fibroblasts to the wound site, acting as repair agents in the healing process.
- Macrophages and Fibroblasts: These cells play crucial roles in tissue repair and collagen synthesis.

Overall, terpenoids play diverse and critical roles in wound healing, ranging from reducing inflammation to enhancing skin permeation and stimulating repair agents [65,66].

Phenolic compounds:

Such as Gallic acid (GA) is derived from the hydrolytic breakdown of tannic acid using a glycoprotein esterase [67,68]. Its beneficial properties include antioxidant, antimicrobial, anti-inflammatory, and anticarcinogenic effects, along with protective impacts on the gastric, cardiac, neurological, and dermal systems [69,70].

Regarding the involvement of GA in wound healing, studies conducted on HaCaT keratinocytes, MEF mouse embryonic fibroblasts, and HF21 human fibroblast cells have shown that GA can directly influence the expression of antioxidant genes and enhance the migration of these cell types under normal and hyperglycaemic conditions. Additionally, GA triggers the activation of key factors essential for wound repair, such as focal adhesion kinases, c-Jun N-terminal kinases, and kinases regulated by extracellular signals [71].

Chitin and Chitosan:

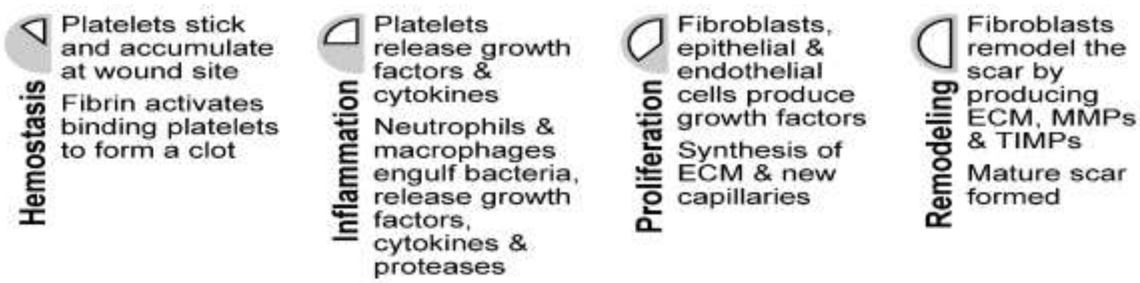

Figure 3: Describes the cellular activities that occur during the four stages of wound healing, namely hemostasis, inflammation, proliferation, and remodeling [139].

Wound healing is a multifaceted biological process that consists of four stages: hemostasis, inflammation, proliferation, and remodeling [72] (figure 3). These stages occur simultaneously [73] and adhere to a specific sequence, which is initiated and regulated by various cell types. While this process typically functions effectively to promote the swift restoration of injured skin, it does not fully regenerate the damaged tissue, often resulting in scarring and the absence of hair follicles or sweat glands in the healed area [74]. The occurrence of impaired wound healing and chronic wounds in certain individuals is not uncommon [72]. A primary goal of wound-healing

advancements is to enhance the healing process, aiming towards tissue regeneration [73,74].

Chitin and its derivatives have demonstrated their utility as components in wound dressings [75,76,77], and have the potential to aid in the creation of skin substitutes that promote skin regeneration by influencing the wound-healing process at a molecular level.

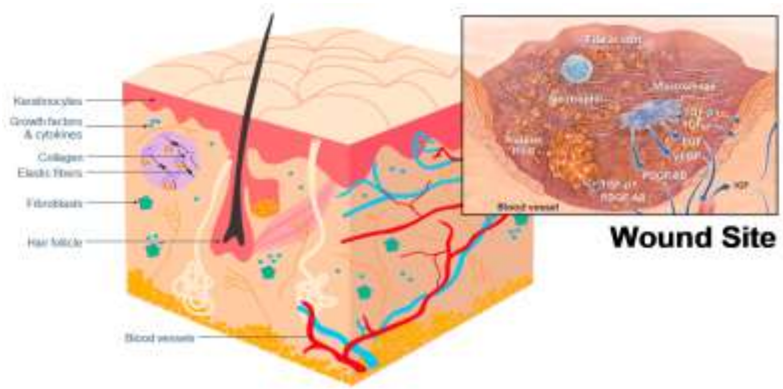

Figure 4: Reorganization of skin and distribution of cells during the wound healing process. Included is an illustration showing the cells involved in the hemostasis and inflammation stages of wound healing, reproduced with permission from Singer and Clark [73].

The hemostasis phase initiates promptly after an injury to stop bleeding by forming a fibrin clot [72] (figure 4). This clot acts as a barrier against external factors and provides a scaffold for cell migration [73]. Chitosan exhibits hemostatic properties by interacting with red blood cells to form a coagulum [78], functioning independently of the regular coagulation mechanism, where red blood cells usually support clot formation [79]. This enhanced hemostatic effect has been observed in various blood conditions, suggesting chitosan's potential to enhance clotting ability and aid in hemostasis [80]. Research has also examined chitosan's efficacy as a hemostatic agent in surgical settings, showing reduced bleeding in wounds treated with chitosan compared to untreated wounds [81,82]. However, comparative studies with other hemostatics and investigations into chitin's hemostatic properties remain unexplored.

After the cessation of hemorrhage, the degranulating fibrin clot and adjacent tissue cells initiate the subsequent phases of healing by releasing cytokines and growth factors, thereby attracting cells to the site of injury [73]. Chitosan has the potential to induce an alternative clotting mechanism, thereby potentially modifying the healing process. Consequently, this alteration may lead to a modified healing response, facilitated by a reduced release of growth factors from the platelets [83]. Neutrophils, also known as polymorphonuclear neutrophils or PMNs, are among the first cells to respond in the subsequent stages. PMNs are responsible for cleaning foreign objects, such as dirt and bacteria, from wounds and eliminating damaged cells. They play a crucial role in causing inflammation [73]. Canine PMNs are attracted to both chitin and chitosan, indicating a positive chemotactic effect [84,85]. A study conducted in vitro demonstrated that chitin has a stronger effect compared to chitosan [85]. However, chitosan has the potential to have a greater impact on the wound as it degrades at a slower rate than chitin [84]. A similar observation has been made in bovine PMNs [86]. In dogs, studies have shown increased infiltration of PMNs after 3 days in wounds treated with chitosan, compared to control wounds. Furthermore, inflammation decreased after 28 days in wounds treated with either chitin or chitosan [87,88]. The surge in PMNs caused by this phenomenon could potentially enhance the cleansing of wounds and expedite the inflammation phase, thereby positively influencing the process of wound healing. Additionally, PMNs have been noted to release pro-inflammatory cytokines, which could stimulate nearby fibroblasts and keratinocytes [74].

Macrophages, which ingest PMNs [89], emerge as the predominant leukocyte during the inflammation phase. They play a crucial role in wound healing by facilitating the transition from inflammation to cell proliferation [72,73]. Macrophages carry out various functions including phagocytosis of dead or infected cells, recruitment of different cells to the wound site, and aiding in the formation of granulation tissue, blood vessels, and the extracellular matrix [73]. Studies have shown that animals lacking macrophages exhibit impaired wound repair. Furthermore, research has indicated that wounds treated with chitosan exhibit increased infiltration of macrophages compared to control wounds, possibly due to chitosan-induced activation of the complement C5, which attracts both macrophages and PMNs [87]. Chitosan has demonstrated the ability to enhance the mRNA expression and synthesis of TGF-β1 and PDGF in macrophages in laboratory settings [90]. Both TGF-β1 and PDGF are known to attract macrophages and fibroblasts, with TGF-β1 also impacting keratinocytes, the outermost layer of the skin [74]. PDGF, on the other hand, stimulates fibroblast proliferation and collagen production [90]. Additionally, it has been observed that 70% deacylated chitin increases the secretion of IL-1 in macrophages, both in vitro [91] and in vivo [92]. This secretion of IL-1 affects fibroblast proliferation [93] and collagen production [87]. However, chitosan (over 95% deacylated) does not exhibit any effect in vitro [91] and has lesser effects than 70% deacylated chitin in vivo [92].

Fibroblasts are essential for wound healing as they create a new skin foundation in the wound. They are responsible for producing the extracellular cell matrix, primarily composed of collagen [73,94]. Collagen is crucial in scar formation, with excessive deposition leading to scars. Conversely, inadequate collagen deposition has been associated with chronic wounds [83].

Therefore, maintaining a balance between collagen production and degradation is vital for complete regeneration. Chitin and chitosan impact the secretion of various cytokines in macrophages, influencing the proliferation of fibroblasts and collagen production. Nevertheless, the impact of chitin and chitosan on fibroblasts is not solely indirect. Chitosan, for instance, triggers an increase in IL-8 production in fibroblasts [86], which serves as a potent chemotactic for PMNs and a regulator of keratinocyte migration and proliferation [93]. Fibroblasts also play a crucial role in generating the extracellular cell matrix. In vitro studies have indicated no direct influence of chitosan on the fibroblasts responsible for producing the extracellular matrix [66]. However, it is plausible that indirect effects through macrophage stimulation, and subsequently fibroblast stimulation, could impact this stage. Additionally, there is a hypothesis that chitin and chitosan could be integrated into the extracellular matrix with the assistance of lysozyme [80], an enzyme capable of breaking down chitin and chitosan.

Unlocking Mushrooms' Healing Abilities for Enhanced Wound Regeneration

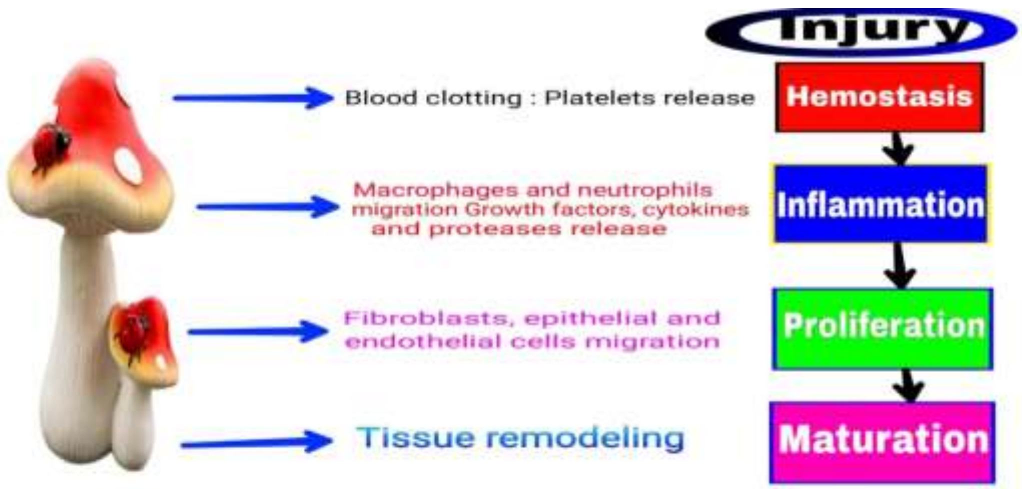

Figure 5: Mushrooms: Facilitating the Wound Healing Process

Wound healing is a natural biological process that can be categorized into four phases: hemostasis (blood clotting), inflammation, proliferation (tissue growth), and maturation (tissue remodeling) [95,96]. The process of wound repair includes various cell types and molecular mediators and is considered a physiological mechanism involving the immune system and the intricate skin repair process [97,98]. Multiple factors can influence the healing of wounds, impacting one or more phases of the process [95]. In essence, wound healing entails an increase in collagen deposition [99] and the regulation of blood platelets for balance and occlusion [100]. Medicinal mushroom extracts and their metabolites have been confirmed to aid in wound healing through various mechanisms, such as stimulating immune epithelial cells, influencing the extracellular matrix, regulating cytokines, growth factors, reactive oxygen species (ROS), and other inflammatory mediators [96, 101]. The effectiveness of the wound-healing process relies heavily on maintaining a balance between pro-inflammatory and pro-regenerative signals, which are controlled by cytokines [102,103] The diagram in Figure 5 provides an overview of the wound-healing process and the involvement of mushrooms in different stages.

Extensive research has been conducted on glucan as a powerful stimulant for macrophages. The 1 → 3 b-glucans found in mushrooms can attract macrophages to the site of a wound, thereby promoting wound healing. It is believed that b-glucans activate macrophages, neutrophils, natural killer (NK) cells, and lymphocytes, thus mediating their effects. Furthermore, studies have shown that b-glucans possess immunostimulatory properties and enhance wound healing by increasing the infiltration of macrophages into the injured area and promoting tissue regeneration [104]. Additionally, b-glucans directly stimulate the synthesis of types I and III collagen [105,106], which aids in collagen regeneration and facilitates wound healing [99]. The combination of b-glucan and collagen matrix wound dressing has been found to reduce the need for various analgesics and dressing changes in children with partial-thickness burns [107].

In an experiment using rats, the combination of beta-glucans from mushrooms and polyvinyl alcohol was found to speed up wound healing by 48% when compared to cotton gauze [108]. Rats with induced ulceration showed increased serum antioxidant enzyme activities and decreased levels of serum mucosal interleukin-2 (IL-2) and tumor necrosis factor (TNF)-alpha when treated with beta-glucans from Ganoderma lucidum and Lentinus edodes [109,110,111]. The promotion of wound healing through the inhibition of TNF-alpha was observed to enhance epithelial cell proliferation and gastric blood flow while reducing epithelial apoptosis [112]. Cell migration in an in vitro scratch assay using Caco-2 cells was enhanced by water-soluble beta-glucans derived from the fruiting bodies of Piptoporus betulinus, as demonstrated [113]. The integrin-induced FAK/Src signaling pathway is believed to play a role in regulating epithelial cell migration [114]. Similarly, beta-glucans from Schizophyllum commune were found to promote re-epithelialization through the integrin/FAK/Src signaling pathway and activate dermal transformation via integrin or ROS production [115]. Various studies have shown that mushrooms possess wound-healing properties due to their high polysaccharide content. For instance, G. lucidum aqueous extract, Ganoderma tsugae [116], and polysaccharides from Agaricus blazei and Phellinus gilvus [117] have been identified as beneficial agents in wound healing, each with distinct mechanisms [101]. The polysaccharides found in G. lucidum can interact with specific receptors or serum-specific proteins on leucocyte surfaces, influencing the activities of macrophages, T-helper cells, NK cells, and other effector cells [118,119].

Furthermore, G. lucidum polysaccharides have been identified as powerful immune-modulating agents [120]. The polysaccharides found in P. gilvus were shown to lower IL-1 expression in the skin of burn wound-treated rats (50 or 100 mg/kg b. w.) [121]. Isolated polysaccharides from P. gilvus were also observed to decrease wound contraction and improve the re-epithelialization of 6-mm circular wounds in streptozotocin (STZ)-induced diabetic rats through topical application twice daily for 5 days [122].

Ganoderma lucidum (G. lucidum) hot aqueous extract was standardized to contain specific components, including total polysaccharides (25.1%), ganoderic acid A (0.45%), and adenosine (0.069%) [126]. In a study conducted on STZ-induced diabetic rats, a 10% aqueous extract cream of G. lucidum was applied to wounds in the posterior neck region. The results showed that the mushroom extract promoted faster wound closure compared to the standard Intrasite gel. Additionally, the treated rats exhibited higher antioxidant activity in their serum, along with reduced levels of oxidative markers, proteins, and lipids. Another research conducted by Gupta et al. (2014) demonstrated that the aqueous lyophilized extract of G. lucidum from the Indian Himalayan region enhanced wound healing efficacy in experimental rats with dermal excision wounds. Furthermore, isolated an immunomodulatory protein called Ling Zhi-8 (LZ-8) from G. lucidum mycelia [131]. Ten microliters of a 1 mg/ml LZ-8 protein solution were applied to the wound in rat liver tissues post monopolar electrosurgery, resulting in a notable improvement in wound healing and a decrease in nuclear factor-kB (NF-kB), caspase-3, and apoptosis. The wound healing potential of aqueous extracts from G. lucidum and Crinipellis schevczenkovi (100 mg powder mycelium/1 ml water for injections) was assessed using the excision wound healing model on albino mice [101]. Administration of C. schevczenkovi mycelium extract resulted in wound healing by the 3rd day, with both extracts achieving complete healing by the 6th day (8th day for the control group).

H. erinaceus, known for its high concentration of b-glucan polysaccharides, has been found to enhance wound healing in laboratory rats (132). The freeze-dried fruiting bodies of H. erinaceus have also shown promise in reducing ulceration in rats with ethanol-induced gastric ulcers when administered as a pre-treatment at doses of 250 and 500 mg/kg b.w. (133). Furthermore, the oral administration of Sparassis crispa, a medicinal mushroom containing over 40% b-glucans, at a dosage of 1,000 mg/kg b.w. per day for a duration of 4 weeks, significantly accelerated wound closure in STZ-induced diabetic rats by promoting collagen regeneration, macrophage, and fibroblast migration, and wound epithelialization [134]. Human dermal fibroblasts have receptors for b glucans, allowing them to directly receive signals from glucans. This direct interaction promotes wound healing by not only activating macrophages but also stimulating fibroblasts [135]. After b-glucan stimulation leads to the activation of two translation factors, activator protein-1 (AP-1) and specific protein-1 (SP-1), as well as two signaling pathways, NF-kB and nuclear factor-1 (NF-1). These activations enhance the immune response, hyperplasia, and the expression of collagen precursor genes [135,136).

The extract of Antrodia camphorata, which is abundant in total polyphenols and flavonoids, has demonstrated remarkable effects in promoting wound healing in rats. This is evidenced by an increase in wound constriction and the accumulation of collagen. Another study has shown that the extract of A. camphorata significantly enhances wound healing both in vivo, as observed by a reduction in inflammatory cells and an increase in collagen synthesis in the injured tissues, and in vitro, by promoting the proliferation of fibroblast cells [96]. In addition, A. bisporus, which contains a high number of polysaccharides, phenolic compounds, and lectin, has been found to be effective in managing wound procedures following glaucoma surgery [101]. The lectin derived from A. bisporus, found in edible mushrooms, was tested on Tenon's capsule fibroblasts in vitro models of wound healing, and it demonstrated a dose-dependent inhibition of proliferation and lattice contraction [137]. Further research on the wound-healing properties of mushrooms can be found in Table 1.

Table 1: Mushrooms' Role in Promoting Wound Healing

Mycological varieties	Active bio-elements	Family	Mechanism of action
Agaricus sylvaticus	crude extract contains proteins, phenols b-glucans, chlorogenic acid, caffeic acid, coumaric acid, and benzoic acid.	Agaricales	Wistar rats showed enhanced wound healing after being treated with 1 ml of gel containing 10% Agaricus sylvaticus for 14 days. The presence of phenols was found to accelerate the healing process [123].
Calvatia gigantean	Unspecified	Agaricaceae	Mushrooms have been discovered to enhance the healing of wounds, and are also successful in addressing stomach discomfort and reducing menstrual pain in women [124].
Podaxis pistillaris	Unspecified	Agaricaceae	Mushrooms accelerate healing wounds [124].
Russula delica	Unspecified	Russulaceae	Mushrooms expedite wound repair [124].
Daldinia concentrica	Crude extract comprises alkaloids, phenol, flavonoids, tannins, terpenoids, and saponins.	Hypoxylaceae	Enhanced wound healing was observed in albino Wistar rats using excision wound model [124]
Agaricusbisporus	Lectin(0–100mg/ml)	Agaricales	In vitro experiments revealed dose-dependent effects on cell proliferation and lattice contraction [125].
Fomes fomentarius	Unspecified	Polyporaceae	The mixture of ash and oil can enhance the healing process of skin wounds. [126].
Ganoderma lucidum	Polysaccharide-rich extract is obtained by combining 5% v/v ethanol absolute methanol, and deionized water.	Basidiomycetes	10% w/w topical application enhanced wound healing in diabetic rats. Triterpenes (0.156 mg/ml) from the extract promoted keratinocyte proliferation and migration safely [126,127].
Phallus impudicus	Unspecified	Phallaceae	Consuming mushrooms improved the healing process of wounds [125].
Termitomyces microcarpus	Powder/paste made from freshly extracted fruiting bodies.	Lyophyllaceae	Enhances the wound healing process [126].
Ganoderma Praelongum	Unspecified	Basidiomycetes	Crude extract has shown significant improvement in the healing process of wounds [127].

CONCLUSION

The study of mushrooms' wound-healing properties shows promise for future therapeutic advancements. Mushrooms contain various bioactive compounds that contribute to their wound-healing effects through mechanisms like anti-inflammatory, antioxidant, antimicrobial, and immunomodulatory activities. Specific mushroom species like *Ganoderma lucidum*, *Hericium erinaceus*, and *Grifola frondosa* have shown potential to speed up wound closure and tissue regeneration. Further research is needed to understand the molecular mechanisms behind mushrooms' wound-healing effects and their applications in clinical settings. Advanced analytical methods can help identify key compounds and pathways involved in wound healing. Clinical studies are necessary to assess the effectiveness and safety of mushroom-based therapies in humans. Randomized controlled trials with standardized mushroom extracts will provide valuable insights into their therapeutic potential. Exploring the synergistic effects of mushrooms with traditional wound-healing treatments could lead to more efficient strategies. Collaboration among researchers, clinicians, and industry partners is crucial for translating promising findings into clinically relevant therapies. In conclusion, mushrooms have significant potential for wound healing, and ongoing research is necessary to fully understand and utilize this potential.

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